REMARKS

Claims 1 to 5 and 7 to 8 are pending. Applicant submits herewith a supplemental Information Disclosure Statement, including a translation of Porta et al. into English for the Examiner's consideration. Claims 1, 4 and 8 have been amended. Amendments to the claims are shown in Appendix I, entitled, "**MARKED UP VERSION OF THE CLAIMS**". Appendix II, showing the claims as pending, is attached for the Examiner's convenience.

Claim 1 has been amended to specify that the panel of two or more monoclonal antibodies have different specificities. Basis for this amendment may be found at page 4, lines 16 to 28 and in the table at page 17 of the specification as filed. Claim 1 has also been amended to specify that the monoclonal antibodies are raised against antigens present on normal cervical tissue. There is basis for this amendment at page 3, lines 9 to 19 of the specification as filed.

Claim 4 has been amended to specify that monoclonal antibodies comprise one or more substances able to bind an antigen which can be bound by at least one of the antibodies deposited. There is basis for this amendment at page 12, lines 11 to 17 of the specification as filed.

Claim 8 has been amended to relate to a monoclonal antibody able to bind to an antigen of cervical tissue to which a monoclonal antibody according to Claim 7 is able to bind. There is basis for this amendment at page 12, lines 11 to 17 of the specification as filed.

Rejections under 35 U.S.C. 102(b)

Claims 1 and 2 are rejected under 35 U.S.C 102(b) as being anticipated by Porta et al. Applicant respectfully traverses.

The claims are directed to a method of screening for a premalignant or neoplastic disease state in a cervical smear sample. The method comprises contacting the sample with a panel of two or more monoclonal antibodies with different specificities and raised against antigens present on normal cervical tissue. Binding of the antibodies to the sample is determined and the binding is compared with a pattern of binding of the antibodies to a

normal cervical cell sample. The antibodies thus detect cellular markers which differ between normal and premalignant or neoplastic cells.

"Anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference... There must be no difference between the claimed invention and the referenced disclosure, as viewed by a person of ordinary skill in the field of invention." Scripps Clinic and Research Foundation v. Genentech, Inc., 18 USPQ 2d 1001.

A translation of Porta et al. into English is submitted herewith for the Examiner's consideration. Also enclosed are copies of Jha et al. 1984 and Epenetos et al. 1982 referred to in Porta et al.

Porta et al. "summarises the most recent and meaningful international data on the use of monoclonal antibodies in cervical cancer." (See abstract). The full paper, Porta et al., summarises Epenetos et al. which discloses the use of two tumour-associated monoclonal antibodies HMFGI and HMFG2 directed against a component of human milk-fat-globule membranes. Epenetos et al. 1982 do not use the monoclonal antibodies in a method of diagnosing cervical cancer, but use the antibodies "to detect primary and metastatic ovarian, breast and gastrointestinal neoplasms." (See Summary of page 1 and table at page 1000).

Porta et al. also summarises Jha et al. This document discloses the use of five monoclonal antibodies with a view to distinguishing between benign and malignant lesions of the cervix. The monoclonal antibodies were raised against antigens present in human milk fat globule membrane, cells derived from a human laryngeal carcinoma and bladder cell lines respectively. The monoclonal antibodies are not raised against antigens present in normal cervical tissue. Tissue samples used were selected from biopsies, rather than smear samples as in the present invention.

Jha et al. teach that monoclonal antibodies stain both normal tissue and neoplastic tissue. Jha et al. conclude that "it is not possible to differentiate neoplastic lesions from benign conditions on the basis of staining." (See page 487 column 1, paragraph 5 of Jha et al.) Porta et al concludes that "on the basis of these observations it does not seem possible to establish an immunohistological differentiation between neoplastic and non-neoplastic epithelium" (see page 6, lines 15 to 16). One skilled in the art would be dissuaded by these

disclosures from using monoclonal antibodies in a method of identifying abnormality in a tissue sample.

Applicant submits, therefore, that Porta et al. do not teach all elements of the claims and respectfully request that the rejection under 35 U.S.C. 102(b) be withdrawn.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Smedts et al. Applicant respectfully traverses.

Claims 1 and 2 are discussed above.

An anticipation rejection requires that all elements and limitations of the rejected claim be taught by a single prior art reference.

Smedts et al. describe a method of examining expression of different keratins using five monoclonal antibodies. The monoclonal antibodies are all raised against synthetic antigens (see page 405, column 1, paragraph 2). Synthetic antigens are not present on normal cervical tissue as specified in Claim 1 as amended.

An important feature of the present invention, now included in Claim 1, is that the monoclonal antibodies are raised against normal cervical tissue. This approach is the opposite to that adapted in the prior art which instead raised antibodies against tumours.

None of the prior art cited or discussed herein uses or suggests the use of monoclonal antibodies raised against normal cervical tissue. Thus, Jha et al. and Epenetos et al. 1982 both refer to antibodies raised against carcinoma or cancer cell lines or agonist or human milk-fat-soluble membranes. Smedt et al. refer to antibodies raised against synthetic antigens.

Because the references do not teach all of the claim elements, the references cannot anticipate the claims. Applicant respectfully requests that the rejection under 35 U.S.C. 102(b) be withdrawn.

Rejections under 35 U.S.C. 103(a)

Claims 1 and 2 are rejected under 35 U.S.C 103(a) as being obvious over Smedts et al. Applicant respectfully traverses.

The claims are discussed above.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Examiner must demonstrate three criteria. First, the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; second, the prior art must provide one of ordinary skill with a reasonable expectation of success; and finally, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. M.P.E.P. § 2143.

Applicant submits that none of the three requirements are met by the rejection. First, one of skill in the art would not have a reasonable expectation of success at arriving at the claimed invention from the teaching of Smedts et al. Applicant submits that the method of Smedts et al. would not work for cervical smear samples. The method relates to testing coherent portions of tissue which have kept their original structure and wherein cells have kept their natural relationship (see page 405, column 1, paragraph 1). For the method of Smedts et al. to be effective, the type of cell being tested must be known, as the staining produced by the monoclonal antibodies is not specific to cervical epithelia, keratins being present in many different epithelia (see page 403, column 2, paragraph 2 and page 405 column 2, paragraph 1). Patterns of keratin distribution are dependent on the cell the keratin is associated with (see left column of Figure 1, page 404). For changes in the keratin distribution to be analysed using the method of Smedts et al., the type of cell tested must thus be known. The method of Smedts et al. would not work for cervical smear samples as cervical smear samples are merely a collection of cells, and one skilled in the art would not be able to tell which type of cell was observed.

Smedts et al. therefore, do not provide a reasonable expectation of success of arriving at the present claims. Additionally, nothing in Smedts et al. provides any motivation to modify Smedts et al. to arrive at the present claims. Finally, all elements of the claims are not taught by the reference. Smedts et al. do not teach the use of antibodies raised against normal cervical tissue antigens. Applicant submits that Claims 1 and 2 are therefore not obvious over Smedts et al.

Claim 8 is rejected under 35 U.S.C.102(b) as anticipated by or in the alternative under 35 U.S.C. 103(a) as obvious over either of Porta et al. or Smedts et al. Claim 8 has been amended to relate to a specific binding substance able to bind to an antigen of cervical tissue to which a specific monoclonal antibody comprising an immunoglobulin antigen binding domain obtained from a hybridoma selected from those deposited is able to bind. Porta et al. discloses monoclonal antibodies raised against carcinoma or cancer cell lines or agonist or human milk-fat-soluble membranes. Smedts et al. disclose monoclonal antibodies directed against individual keratin polypeptides. Neither of these references teach or suggest a specific binding substance able to bind to an antigen of cervical tissue to which a hybridoma selected from those deposited can bind. Applicant submits, therefore, that a rejection based on either anticipation or obviousness is not supported by the references. Claim 8 is novel and inventive over the prior art cited, and Applicant respectfully requests that the rejection be withdrawn.

Rejections under 35 U.S.C. 112, first paragraph

Claims 1 to 4 are rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicant respectfully traverses.

Applicant submits that it is clear from the specification as filed that the staining pattern is significantly different between premalignant and normal specimens. At page 12, lines 11 to 15 teaches that one or more of antibodies may be used in the method of the present invention. The disclosure made at page 3, lines 9 to 19 of the specification as filed teaches that "antibodies ... may be used in the qualitative and/or quantitative detection of marker antigens on the cells, enabling increased or reduced expression or loss of one or more of the markers to be correlated with a disease (or pre-disease) state." This disclosure clearly supports the use of antibodies that differ in their binding patterns between normal and disease cells. The Examples support this disclosure. Tables 3 and 4 compare the binding of the monoclonal antibodies of the Examples to normal cervical smears compared to pre-malignant specimens. One skilled in the art would be aware that –ve and +ve are common abbreviations of negative and positive respectively.

An important aspect of the present invention is that the monoclonal antibodies are raised against antigens present on normal cervical tissue. Table 3 illustrates this, as there is some binding of the monoclonal antibodies with normal cervical smear samples. The pattern of binding differs between normal and premalignant cervical smears. This can be seen from the difference in binding between Tables 1 and 2. The mainly negative binding results for parabasal cells may indicate that no parabasal cells are present in the smear samples tested.

The present invention is concerned with identifying samples with some deviation from normality to be identified and examined further. Suspect samples are highlighted for further examination by suitably qualified personnel (see page 3, lines 19 to 23 of the specification as filed). Diagnosis and decisions on the need for and nature of treatment remain in the domain of clinicians. (See page 3, lines 27 and 28 and page 4, line 1).

Applicant submits, therefore, that the claims are clearly enabled by the specification, and respectfully request that the rejection be withdrawn.

Claims 1, 2 and 4 are rejected under 35 U.S.C 112, first paragraph as containing subject matter which was not described in the specification as filed in such a way as to reasonably convey that the inventor had possession of the claimed invention. Claim 1 has been amended and now specifies that the sample is contacted with a panel of two or more monoclonal antibodies having different specificities. This amendment is clearly supported by the Table at page 17 of the specification as filed. Applicant respectfully requests that the rejection be withdrawn

Rejections under 35 U.S.C. 112, second paragraph

Claims 1, 2 and 4 are rejected under 35 U.S.C.112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant submits that the amendments made to these Claims overcome this objection, and request that the rejection be withdrawn.

CONCLUSION

It is therefore believed that the Examiner's rejections have been overcome by the amendments, and issuance of the Patent is therefore respectfully solicited. If, upon review, the Examiner feels there are additional outstanding issues, Applicant respectfully requests that the Examiner call the undersigned attorney.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON HERBERT, LLP

Anne M. Shyjan, Reg. No. 47,086 for
Richard F. Trecartin, Reg. No. 31,801

Four Embarcadero Center
Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989

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APPENDIX I: MARKED UP VERSION OF THE CLAIMS

2. (THREE TIMES AMENDED) A method of screening for a premalignant or neoplastic disease state in a cervical smear sample containing cells of the cervix, the method comprising contacting said sample with a panel of two or more monoclonal antibodies ~~with said sample, each antibody having specificity for a different antigen of said sample relative to the other antibodies in said sample~~ having different specificities and raised against antigens present on normal cervical tissue, determining binding of said monoclonal antibodies to said sample and comparing the binding with a pattern of binding of said monoclonal antibodies to a normal cervical cell sample, wherein said monoclonal antibodies detect cellular markers which differ between normal and premalignant or neoplastic cells.

4. (FOUR TIMES AMENDED) A method according to Claim 1 wherein the monoclonal antibodies comprise one or more substances able to bind an antigen which can be bound by ~~monoclonal antibodies which specifically compete for binding to cervical cells with~~ one or more antibodies obtained from a hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

8. (THREE TIMES AMENDED) A specific monoclonal antibody able to bind to an antigen of cervical tissue to which ~~which specifically competes for binding to cervical tissue with~~ a monoclonal antibody according to Claim 7 is able to bind.

APPENDIX II: PENDING CLAIMS

1. (THREE TIMES AMENDED) A method of screening for a premalignant or neoplastic disease state in a cervical smear sample containing cells of the cervix, the method comprising contacting said sample with a panel of two or more monoclonal antibodies having different specificities and raised against antigens present on normal cervical tissue, determining binding of said monoclonal antibodies to said sample and comparing the binding with a pattern of binding of said monoclonal antibodies to a normal cervical cell sample, wherein said monoclonal antibodies detect cellular markers which differ between normal and premalignant or neoplastic cells.

2. (AMENDED) A method according to claim 1 wherein the monoclonal antibodies comprise one or more polypeptides each comprising an antigen binding domain.

3. (TWICE AMENDED) A method of determining a premalignant or neoplastic disease state in a cervical smear sample containing cells of the cervix, the method comprising contacting one or more monoclonal antibodies with said sample, determining binding of said monoclonal antibodies to said sample and comparing the binding with a pattern of binding of said monoclonal antibodies to a normal cervical cell sample, wherein said monoclonal antibodies detect cellular markers which differ between normal and premalignant or neoplastic cells and wherein the monoclonal antibodies comprise one or more polypeptides each comprising an antigen binding domain obtained from a hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

4. (FOUR TIMES AMENDED) A method according to Claim 1 wherein the monoclonal antibodies comprise one or more substances able to bind an antigen which can be bound by one or more antibodies obtained from a hybridoma selected from those deposited at the

European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

5. (AMENDED) (ALLOWED) A hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

7. (AMENDED) (ALLOWED) A specific monoclonal antibody comprising an immunoglobulin antigen binding domain obtained from a hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

8. (THREE TIMES AMENDED) A specific monoclonal antibody able to bind to an antigen of cervical tissue to which a monoclonal antibody according to Claim 7 is able to bind.